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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,270	CHANG ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8-12-03* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28 and 30-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28 and 30-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed 8-12-03 has been entered. Claims 1, 19 and 30 have been amended. Claims 33-39 have been added. Claims 1-28 and 30-39 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-28 and 30-32 remain rejected and claims 33-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivering Tf-Adp53 vector expressing p53 to SCCHN xenograft on the lower back above the tail of nude mice via intravenous injection and reduction of tumor size while combined with radiation treatment, and delivering said Tf-Adp53 vector to immune competent B16 mouse of melanoma lung metastases model and reduction of lung metastases while combined with chemotherapy, does not reasonably provide enablement for a vector comprising a ligand other than transferrin non-covalently bound to a virus expressing a gene other than p53, a method for providing said vector to an animal for treating head and neck cancer, bladder cancer, breast cancer, thyroid cancer, ovarian cancer, prostate cancer, melanoma or lymphoma with or without combination with radiation or chemotherapy, and a method for providing Tf-Adp53 to an animal for treating brain tumor with or without combination with radiation or chemotherapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the

invention commensurate in scope with these claims and is repeated for the reason set forth in the preceding Official action mailed 2-12-03. Applicant's arguments filed 8-12-03 have been fully considered but they are not persuasive.

Applicants argue that the declaration filed 12-10-02 described preparation of vectors using molecules other than transferrin, and the methods for preparing vectors comprising three different ligands, two different genes and three different viruses, i.e. adenoviruses, retroviruses, and Herpes simplex viruses have been provided. Applicants further argue that ligands can be proteins, peptides, hormones, antibodies and antibody fragments and selection of a suitable ligand is a matter of routine experimentation, and EGF receptor, estrogen, and FGF receptor are known in the art to be over-expressed in a variety of cancers (amendment, p. 10-13). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 2-12-03. As discussed in the preceding Official action mailed 2-12-03, the specification states that "The present invention relates to improvements to gene transfer and gene therapy technology. More specifically, the invention provides composition and methods for targeted *in vitro* and *in vivo* viral delivery of nucleic acids into human and other animals to a specific organ, tissue, or tumor" (page 1, lines 6-9). The claims read on gene transfer in vivo and the only use for the claimed vectors as disclosed in the specification is to improve gene transfer and gene therapy technology. The claims encompass a vector comprising any cell-targeting ligand non-covalently directly bound to a virus expressing any gene, and a method for providing said vector to an animal for treating **head** and neck cancer, bladder cancer, breast cancer, thyroid cancer, ovarian cancer, prostate cancer, melanoma or lymphoma with or without combination with radiation or chemotherapy *in vivo*. The preceding Official action does not argue whether the vectors can be

made rather the Official action points out that the use of the claimed vectors for gene transfer or improving gene transfer in vivo is not enabled. The claims include use of numerous ligands for gene transfer of a virus comprising a therapeutic nucleic acid to various target cell types in vivo. A ligand mediated cell targeting can only succeed when the ligand is used for delivering a therapeutic gene to a tumor type over-expressing the ligand receptor. Although expression of some ligand receptors on different cancer cells were known in the art, however, the specification fails to provide sufficient enabling disclosure for the full scope of the invention claimed.

As discussed before, the fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell affect the efficiency of gene transfer in vivo. The specification fails to provide adequate guidance and evidence for how to deliver or improve delivery efficiency of the claimed vectors to various types of cancers, including brain tumor, in an animal, such as a human, via various administration routes so as to provide therapeutic effects in vivo. Further, the specification only discloses delivering Tf-Adp53 vector expressing p53 to SCCHN xenograft on the lower back above the tail of nude mice via intravenous injection and reduction of tumor size while **combined with radiation treatment**, and delivering said Tf-Adp53 vector to immune competent B16 mouse of melanoma lung metastases model and reduction of lung metastases while **combined with chemotherapy.** The specification indicates that "As in Example 4, the tumors in the untreated animals and those receiving targeted Ad-p53 without radiation

demonstrated continuous growth" (see page 19, lines 12-14). It appears that delivery of a vector comprising a p53 nucleic acid alone fails to provide therapeutic effects in vivo and there is no evidence of record that the claimed vectors provide improved gene transfer efficiency for gene therapy in vivo. Thus, in view of the reasons set forth above, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the claimed invention is a simplified and efficient targeting method for getting a virus to a tumor site and claim 19 specifies cancers as head and neck cancer, bladder cancer etc., and do not include brain cancer (amendment, p. 14, 15). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 2-12-03 and the reasons set forth above. The "target cell" in claim 1 encompasses brain cancer cells and the "head and neck cancer" in claim 19 includes brain cancer. Thus, the claimed invention read on delivering the vector to brain cancer cells in vivo.

Applicants argue that claim 19 encompasses the treatment of humans but does not specify that human are to be treated. Applicants cite references Shimada et al., Swisher et al., 2003, 2002, Makower et al., Pagliaro et al., Chada et al., and US patent No. 6,410,010 and argue that using nucleic acid encoding p53 was well-established in the art of gene therapy and clinical trials for treating cancers are undergoing (amendment, p. 16, 17). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 2-12-03 and the reasons set forth above. Claim 19 encompasses treating human and claim 20 specifies treating human. The specification fails to provide adequate guidance and evidence for how to deliver the claimed vector to a human for treating various cancers, such as breast cancers, prostate cancers, brain

tumors etc., and said delivery would result in sufficient expression of the therapeutic product so as to provide therapeutic effect said human. The cited references either provide in vitro data of cancer cell treatment or present in vivo data via intratumoral injection, intralesional injection, or intravesical instillation. Those references fail to provide evidence of treating various cancers with vectors comprising a nucleic acid encoding p53 via administration route other than in situ administration such that expression of p53 protein provide therapeutic effects in vivo. As discussed in the preceding Official action mailed 2-12-03, gene transfer *in vivo* and vector targeting to desired tissues *in vivo* were unpredictable at the time of the invention. The in vitro data can not be extrapolated to success for gene therapy in vivo, and each gene therapy protocol has to be considered case by case. One successful gene therapy or gene transfer in vivo can not be extrapolated to success for another gene therapy in vivo. Furthermore, the specification indicates that "As in Example 4, the tumors in the untreated animals and those receiving targeted Ad-p53 without radiation demonstrated continuous growth" (see page 19, lines 12-14). It appears that delivery of a vector comprising a p53 nucleic acid alone via intravenous injection fails to provide therapeutic effects in vivo and there is no evidence of record that the claimed vectors provide improved gene transfer efficiency for gene therapy in vivo via various administration routes.

Applicants argue that the present invention represents an advance over the present vector delivering methods and the targeting entity is not chemically conjugated to the virus and no linker molecule is involved (amendment, p. 17, 18). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 2-12-03 and the reasons set forth above.

Applicants argue that it was known in the art that most tumors over-express transferin and transferin is a well-accepted tumor targeting ligand (amendment, p. 19, 20). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 2-12-03 and the reasons set forth above.

Applicants argue that mouse models were used for human cancers and the present invention is not the development of a new therapeutic agent but a method for targeting a therapeutic agent to target cells. Applicants further argue that p53 is nonfunctional in a majority of cancers and a viral vector comprising the p53 gene is therapeutically useful and it is routine experimentation to determine other useful targeting ligand for a viral vector comprising a therapeutic nucleic acid. Applicants argue that the cited Eck reference refer to unliganded, non-directed viral vectors and the specification shows intravenous and intratumoral delivery of the vectors (amendment, p. 21, 22). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 2-12-03 and the reasons set forth above.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-4, 6, 8-11, 17 and 18 remain rejected and claim 34 is rejected under 35 U.S.C. 102(b) as being anticipated by Douglas et al., 1997 (International Journal of Oncology, Vol. 11, p. 341-348) and is repeated for the reasons set forth in the preceding Official action mailed 2-12-03. Applicant's arguments filed 8-12-03 have been fully considered but they are not persuasive.

Claim 34 specifies the virus is an adenovirus and the ligand is an antibody fragment.

Applicants argue that Douglas does not teach a ligand non-covalwntly bound directly to the virus rather Douglas teaches binding ligand through a neutralizing Fab fragment of a monoclonal antibody (amendment, p. 22, 23). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 2-12-03. The neutralizing Fab fragment of an anti-knob monoclonal antibody is also considered a ligand and said Fab fragment is complexed to the adenovirus.

5. Claims 1-4, 6, 8-10, 12, 17 and 18 remain rejected under 35 U.S.C. 102(e) as being anticipated by Woo et al., 1999 (US Patent 5,994,109) and is repeated for the reasons set forth in the preceding Official action mailed 2-12-03. Applicant's arguments filed 8-12-03 have been fully considered but they are not persuasive.

Applicants argue that the system taught by Woo has three parts, ligand, binding molecule and DNA and the binding molecule noncovalently links to a nucleic acid and covalently links to a surface ligand but do not teach or suggest directly and non-covalently binding a ligand to a virus. Applicants argue that in some examples the adenovirus does not serve to provide nucleic acid to be delivered (amendment, p. 24, 25). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 2-12-03. Woo teaches the binding molecule can

non-covalently bind to nucleic acid, such as viruses, and the binding molecule also can covalently link to a ligand. The binding molecule includes polylysine, polyamines and **cationic peptides** etc. (Column 6). The cationic peptide is considered a ligand, which can non-covalently bind to viruses, and it can bind to other ligand for cell-specific delivery of nucleic acid. Therefore, Woo does teach a ligand non-covalently and directly linked to a virus.

Conclusion

No claim is allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.